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10/030,003	05/28/2002	Maurizio Zanetti	P-ZA 5015	5749

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 05/02/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/030,003	ZANETTI, MAURIZIO	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 February 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-43 and 45-50* is/are pending in the application.

4a) Of the above claim(s) *9,10,24,25,36,37 and 45-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8, 11-23, 26-35, and 38-43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response received on 2/13/06 has been entered. Claim 44 has been canceled. Claims 1-43 and 45-50 are pending in the instant application. This application contains claims 9-10, 24-25, 36-37, and 45-50 drawn to an invention nonelected **without** traverse in the response filed on 2/16/05. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01. Claims 1-8, 11-23, 26-35, and 38-43 are currently under examination in the instant application. An action on the merits follows. Those sections of Title 35, US code, not included in this action can be found in the previous office action. Please note that as per the elected invention, the claims have been examined based on the elected species (c), one or more epitopes contained within the CDR of an immunoglobulin molecule", no allowable generic claim being present in the instant application.

Nucleotide and/or Amino Acid Sequences

Applicant's amendment to the specification inserted the appropriate SEQ ID NOS listed in the paper copy and CRF of the sequence listing next to the various amino acid and nucleic acid sequences disclosed in the specification. As such, this application is now in compliance with the requirements of 37 CFR 1.821 through 1.825.

Double Patenting

The provisional rejection of pending claims 1-8, 11-23, 26-35, and 38-43 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 38-44 of copending Application No. 09/300,959, hereafter referred to as the '959 application, is maintained. Applicant's have asked that his rejection be held in abeyance until the indication of allowable subject matter. Since applicant's have not traversed the grounds of rejection, therefore the rejection of record is maintained. However, as indicated, this is a provisional rejection as the co-pending application has not been allowed.

Claim Rejections - 35 USC § 112

The rejection of pending claims 1-8, 11-23, 26-35, and 38-43 under 35 U.S.C. 112, first paragraph, because the specification, for scope of enablement is maintained in part. It is noted that applicant's amendments to the claims to recite a B cell specific expression element overcomes the previous rejection concerning the lack of enablement for the use of any hematopoietic cell-specific expression element. Regarding the remaining grounds of rejection, applicant's amendments and arguments have been fully considered but have not been found persuasive in overcoming the these grounds of rejection for reasons of record as discussed in detail below.

The previous office action indicated the following subject matter enabled by the specification as written: the specification, while being enabling for a DNA plasmid comprising an immunoglobulin heavy chain enhancer/promoter operatively linked to an immunoglobulin

molecule containing one or more heterologous antigenic epitopes inserted within one or more CDR of the immunoglobulin molecule, and methods of stimulating an immune response *in vivo* by intrasplenic injection of a plasmid DNA comprising an immunoglobulin heavy chain enhancer/promoter operatively linked to an immunoglobulin molecule containing one or more heterologous antigenic epitopes inserted within one or more CDR of the immunoglobulin molecule, does not reasonably provide enablement for the use of any nucleic acid comprising a B cell-specific expression element operatively linked to an immunoglobulin molecule containing one or more heterologous antigenic epitopes inserted within one or more CDR of the immunoglobulin molecule acids to generate immune responses by administering the nucleic acids to any lymphoid tissue or cell *in vivo* or *ex vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The applicant argues that the alleged unpredictability asserted in the previous office action does not apply to the claims as amended which are now limited to the use of B cell specific expression elements and further recite that the epitopes are expressed in a B cell. This is not agreed. The previous office action set forth several grounds of rejection based on the breadth of the nucleic acids claimed, the breadth of the route of administration of nucleic acid *in vivo*, the unpredictability in targeting a specific cell type *in vivo* and the unpredictability that a single cell type, such as a B cell, would be capable of inducing an immune response. Applicant's amendments, while overcoming the use of any hematopoietic cell expression element, as noted above, does not overcome any of the other issues raised in the previous office action. Further, the limitation that the epitopes are expressed in a B cell does not overcome the issues related to the

unpredictability of targeting B cells *in vivo* in blood or other lymph tissue using any route of administration, the unpredictability of using any nucleic acid expression system to target B cells *in vivo* and the lack of predictability that B cells in particular are capable of stimulating therapeutic immune responses using applicant's claimed *ex vivo* or *in vivo* methods. The applicant has not specifically addressed any of the detailed scientific reasons or references cited in support of unpredictability presented in the previous office action, see in particular Verma et al., Orkin et al., Marshall et al., Miller et al., and Deonarian et al. The applicant simply points to pages 15 and 31-32 of the specification for its teachings that the methods claimed can be used to deliver nucleic acid to various secondary lymphoid tissues and that delivery methods can include direct injection or *ex vivo* transfer. However, the teachings of the specification were analyzed in direct accordance to the factors outlined in *In re Wands*, namely 1) the nature of the invention, 2) the state of the prior art, 3) the predictability of the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of the skilled artisan, and 8) the breadth of the claims, and were not found to enable the scope of the instant methods.

Finally, the applicant argues that it is irrelevant whether B cells alone or other cells present in the spleen are responsible for the observed responses in applicant's working examples since all that is required for the method as claimed is that the B cells express the epitopes resulting in an immune response. In response, while it is agreed that the working examples enable the direct injection of plasmid DNA into spleen wherein the expression of the recited epitopes in B cells present in the spleen result in an immune response, the previous office action presented detailed scientific reasons why the splenocyte population of cells is substantially

different from other lymphoid cell populations or blood such that applicant's success with intrasplenic injection of plasmid DNA cannot be extrapolated to other routes or administration of the DNA or the administration of *ex vivo* modified B cells. Specifically, the previous office action explained that it is unclear using intrasplenic injection whether the B cell themselves are responsible for the observed responses, or whether antigen shed from the B cell is picked up by other types of cell in the splenocyte population which then stimulate immune responses, or whether it is a combination of the two. In addition, while splenocytes contain large numbers of B cells, other lymphoid organs do not. If B cells are responsible for the observed immune stimulation, then it is unpredictable whether a population of lymphoid cell derived from urogenital tissue or lymph nodes, which contains significantly less B cells than spleen, would be capable of stimulating effective immune responses against encoded antigen. Further, if the immune response results from activation by other types of antigen presenting cells present in the spleen that take up shed antigen, it is unclear whether other lymphoid organs or blood comprise they cell types in sufficient numbers to stimulate an immune response. Thus, based on the number of different cell types found in lymphoid tissue, the differing composition of cell types between different lymphoid tissues, the unpredictability in the art concerning which types of antigen presenting cells are responsible for stimulating T and B cells responses, the limitation of the working examples to transfected splenocytes, and the breadth of the claims, it would have required undue experimentation for the skilled artisan to practice the breadth of the claims as written.

Therefore, for reasons of record, the rejection is maintained.

The rejection of claims 1-8, 11-16, and 38-44 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in view of applicant's amendments to the claims.

However, applicant's amendments have necessitated the following new grounds of rejection of the claims under 35 U.S.C. 112, second paragraph as follows.

Claims 3, 18, and 35 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3 and 18 have been amended to recite, ".. wherein said expression element functions in a cell selected from a group consisting of B cell". As amended, the claims no longer list a "group" since only a single embodiment is recited, the B cell. As such, selecting from a group which consists of a single member is confusing. Further, since the independent claims from which claims 3 and 18 depend have also been amended to recite a "B cell-specific expression element", claims 3 and 18 do not appear to further limit the parent claims as a B cell-specific expression element by definition functions in a B cell.

Claim 35 recites, "..wherein said expression element functions in a cell selected from a group consisting of B cell and T cell". However, claim 32, from which claim 35 depends, has been amended to recite a "B cell-specific expression element". Therefore, since the parent claim limits the expression element to one which is specific for a B cell, the limitation of claim 35

which states that the expression element functions in a T cell conflicts with the limitation in the parent claim.

Claim Rejections - 35 USC § 102

The rejection of claims 32-33, 35, 38-39, 41-42, and 44 are rejected under 35 U.S.C. 102(b) as being anticipated by Xiong et al. (1997) Nat. Biotech., Vol. 15, 882-886, is maintained over pending claims 32-33, 35, 38-39, and 41-42 and withdrawn over canceled claim 44. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

The applicant argues that Xiong et al. does not anticipate the instant invention as claimed because Xiong et al. exemplifies a B cell epitope and a T cell epitope cloned separately into CDR2 and CDR3, citing page 885 of Xiong. Thus, the applicant concludes that Xiong et al. does not teach two or more T cell epitopes, or two or more T cell epitopes in a CDR.

In response, the rejection of record clearly points to where Xiong et al. teaches that the two epitopes inserted into the CDRs can be a T helper epitope (i.e. a CD4 epitope) and a B cell epitope, or a T helper epitope and a CTL epitope (i.e. a CD8 epitope) (Xiong et al., page 885, column 1, paragraph 2). Further, regarding the argument that Xiong does not teach that the two epitopes are cloned into a CDR, the applicant appears to be interpreting the language in claim 38 to limit the invention to wherein both or all of the T cell epitopes are inserted into the same CDR. However, claim 38 is not so limited. The applicant is pointed to original claim 44, which depended on claim 38, and which recited that the epitopes were inserted into two CDRs.

Although applicant has canceled claim 44, claim 38 has not been amended from the original in terms of its recitation regarding the positioning of the epitopes. Thus, it is clear that claim 38 continues to read on insertion of epitopes into more than one CDR. As such, it is maintained that Xiong et al. does teach each an every limitation of the claims as written and therefore anticipates the instant claims.

Claim Rejections - 35 USC § 103

The rejection of claims 1-8, 11-23, 26-35, and 38-44 under 35 U.S.C. 103(a) as being unpatentable over Xiong et al. (1997) Nat. Biotech., Vol. 15, 882-886, in view of US 5,969,109 (10/19/99), hereafter referred to as Bona et al., and US 2002/0007173 A1 (1/17/02), hereafter referred to as Kundig et al., is maintained over pending claims 1-8, 11-23, 26-35, and 38-43, and withdrawn over canceled claim 44. Applicant's arguments have been fully considered but have not been found persuasive in overcoming the instant grounds of rejection for reasons of record as discussed in detail below.

Regarding claims 17-23, 26-31, 32-35 and 38-43, the applicant argues that Xiong et al. does not teach two T cell epitopes within a CDR and that Bona and Kundig do not supply the missing teachings. Applicant's arguments regarding Xiong et al. were addressed in detail above and were not found persuasive. As stated above, Xiong et al. does in fact teach that the two epitopes inserted into the CDRs can be a T helper epitope (i.e. a CD4 epitope) and a B cell epitope, or a T helper epitope and a CTL epitope (i.e. a CD8 epitope) (Xiong et al., page 885,

column 1, paragraph 2). Further, as noted above, neither of claims 17 or 38 are limited to the insertion of the epitopes into the same CDR.

Regarding claims 1-8, and presumably 11-16, the applicant argues none of Xiong et al. Kundig et al. or Bona et al. teach administering nucleic acids to B cells *ex vivo* and administering the B cells to an individual to stimulate and immune response.

In response, while claim 1, as amended, now recites that B cells expressing said heterologous epitopes are administered to an individual, it is maintained that the combination of the teachings of the cited references renders the instant claims as amended *prima facie* obvious. The rejection of record cited Kundig for teaching *ex vivo* methods to stimulate an immune response. While Kundig et al. does teach administering antigen presenting cells comprising a nucleic acid encoding a heterologous antigenic peptide/protein in an individual to generate immune responses, and specifically teaches using dendritic cells as the antigen presenting cells, it is acknowledged that Kundig does not specifically teach using B cells (see Kundig et al., page 3, column 2, paragraphs 33 and 34). However, Xiong et al. provides motivation for administering B cells rather than dendritic cells as Xiong et al. teaches to use a B cell specific immunoglobulin promoter to express the encoded heterologous epitopes and further teaches that the target cells for transfection are B cells (Xiong et al., page 882, column 1, paragraph 1). Therefore, in view of the teachings of Kundig et al. that antigen presenting cells comprising nucleic acids can be used in lieu of nucleic acids alone for immunization, and the teachings and motivation provided by Xiong et al. to target expression of the epitopes to B cells in order to stimulate immune responses, it would have been *prima facie* obvious to the skilled artisan at the time of filing to administer antigen presenting B cells comprising a nucleic acid encoding the heterologous

epitope(s) to an individual to stimulate an immune response with a reasonable expectation of success.

Therefore, for reasons of record, the rejection is maintained.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Dave Nguyen, can be reached at (571) 272-0731. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology

center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197. Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

ANNE M. WEHBE' PH.D
PRIMARY EXAMINER